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REVIEW ARTICLE

Role of cerebrovascular risk factors in dementia

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Abstract

With the rapid increase in the prevalence of dementia worldwide there has been significant research into modifiable risk factors for dementia. In this regard cerebrovascular diseases (CVD) represent a potential therapeutic target in the fight against the epidemic of dementia. Both large vessel CVD and small vessel disease in the form of chronic lacunes, white matter hyperintensity, microbleeds, and perivascular spaces have been strongly associated with the risk of developing dementia. These CVD factors may initiate or accelerate the amyloid and tau cascades resulting in greater rates of neurodegeneration and dementia. Understanding the precise mechanisms for the interaction between CVD and neurodegeneration will allow development of potential interventional targets. These CVD risk factors may be of particular relevance to the Asian population where a high burden of small vessel CVD has been demonstrated in Asian patients with dementia.

INTRODUCTION

Dementia is a clinical syndrome characterized by chronic and progressive deterioration of mental functioning and impaired daily functioning.[1]Cerebrovascular disease (CVD) has been observed to be attributable to two of the leading causes of dementia worldwide – Alzheimer's disease (AD) and vascular dementia (VaD).[2] In a recent study by Kandiah *et al*., severity of AD was associated with increased burden of CVD pathology.[3]

CVD comprises of a group of vascular pathologies that compromises cerebrovascular circulation, resulting in hypoperfusion and ischemic injury. One subtype called cerebral small-vessel disease affects the small perforating arterioles, capillaries, and venules, leading to damage in the brain parenchyma.

We highlight the global prevalence of dementia, particularly AD and VaD; risk factors for CVD and their contributory role; role of large vessel CVD in the progression of dementia; role and pathophysiology of cerebral small-vessel disease; and the current treatment and preventive measures.

INCIDENCE AND PREVALENCE OF DEMENTIA

The prevalence of dementia is constantly on the rise worldwide. As of 2010, 35.6 million people have been diagnosed. This figure is projected to double every 20 years and reach 115.4 million by 2050[1], with low-to-middle income regions of the world expected to bear the brunt of the burden. Regional differences in prevalence rates of dementia may be attributed to poorer allocation of resources towards prevention strategies, discrepancies in diagnostic assessment, low community outreach, and cultural stigma.[4]

The incidence rate of dementia is approximately 4.6 million cases a year, with China and its western-Pacific neighbors expected to confer the greatest proportion of new cases.[5] A pooled-analysis of eight population-based studies in Europe reported that AD and VaD contribute 60-70% and 15-20% of new cases of dementia respectively, with increased rate of incidence until the age of 85. After which, incidence rates increased for women only, highlighting sex-related differences in survivability.[6]

CEREBROVASCULAR RISK FACTORS

Approximately half of all AD cases worldwide can be attributed to cerebrovascular risk factors (CVRF) such as hypertension, diabetes mellitus, hyperlipidemia, smoking, alcohol intake, and obesity. Approximately 9% of all cases of dementia may be preventable if increased

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measures had been taken to reduce the global prevalence of CVRF.[7]

Hypertension

In recent years, considerable research has shifted its focus towards hypertension specifically at midlife. Approximately 5% of AD cases can be ascribed to midlife hypertension.[7] High systolic blood pressure at midlife is an independent risk factor for late-life cerebral atrophy, cognitive decline, and dementia[8], even at 30 years prior to VaD diagnosis.[9]

Diabetes mellitus

An estimated 285 million adults worldwide were living with diabetes mellitus (DM) as of 2010, and about 2% of all AD cases can be ascribed to DM.[7] The annual incidence of DM is estimated to be 1% among people over the age of 70 years.[10] This incidence rate is expected to have a significant impact on dementia research that have longitudinal designs with lengthy interval periods, therefore studies must be interpreted with caution as there is a risk for an overestimation of prevalence. Compared to those without, a person with DM has an increased risk of developing dementia, especially AD.[11] In addition, an interaction with APOE4 genotype was found whereby carriers were found to be at double the relative risk of developing dementia.[10]

Hypercholesterolemia

In the United States, an estimated 31.9 million adults over the age of 20 years are recognized as having high serum total cholesterol (≥240 mg/dL).[12] While the dominant view prevails that high total cholesterol is a significant risk factor for dementia especially at midlife[13], contesting this view is evidence that hypercholesterolemia may confer a protective role against cognitive decline and dementia.[14] However, this protective association may be moderated by late-life hypercholesterolemia[15] or confounded by the effect of high-density lipoprotein (HDL) which is hypothesized to have anti-inflammatory properties and delay the onset of dementia.[16]

Smoking

Tobacco use contributes to 14% of all reported cases of AD.[7] One mechanism by which smoking leads to increased risk for dementia is postulated to be through vascular disorders such as atherosclerosis and other forms of CVD.[17] This would then induce cerebral hypoperfusion which is associated with cognitive decline and dementia.[18] However, the relationship between smoking and dementia has remained inconclusive, with some studies asserting a risk for cognitive impairment and dementia while others argue for a protective role.[19] The protective effect may be attributed to cognitive enhancement via nicotinic receptor activity in the cholinergic pathways[20] or sheer survival bias.

Alcohol

A large meta-analysis suggested a dose-dependent relationship between alcohol intake and dementia: low levels of alcohol intake confer a protective role for dementia and conversely, high levels of alcohol akin to alcohol abuse increase the risk for dementia.[21] The protective role of light alcohol intake may be attributed to improvements in cardiovascular health such as raising concentrations of HDL. Frequency and level of alcohol consumption could be mediated by lifestyle, socioeconomic status, and a country's economic wealth which is strongly associated with prevalence of heavy episodic drinking.[22,23]

Obesity

As of 2014, approximately 600 million adults over the age of 18 years were considered obese (≥30 BMI), with a higher prevalence of obesity in women globally.[7] Obesity poses as a significant risk factor for both incident AD and VaD. Beydoun *et al*. also highlight a U-shaped relationship between BMI and dementia whereby obese and underweight individuals are at an increased risk for dementia, and the need to consider lifestyle and mental health factors that accompany obesity such as physical inactivity and depression.[24]

LARGE VESSEL CEREBROVASCULAR DISEASE AND DEMENTIA

Intracranial atherosclerosis

Intracranial atherosclerosis is a chronic disease of the large arteries that involves a build-up of plaque along the vessel wall that can present symptomatically or asymptomatically[25,26], with the circle of Willis as the primary target.[27] People of Asian, African, or Hispanic ancestry are at a higher risk of developing intracranial atherosclerosis compared to caucasians.[25]

In the Rotterdam study, degree of atherosclerotic burden was associated with increased risk for all

dementias. Moreover, participants positive for APOE4 genotype and a moderate-to-severe degree of atherosclerotic burden were at even greater risk for all dementias.[28] In an Asian cohort of stroke patients, intracranial stenosis was shown to be correlated to burden of post-stroke dementia.[29] Greater atherosclerotic burden of the circle of Willis has been reported to be greater in patients with AD.[30] This is consistent with the evidence for increased risk for pathological lesions of AD only –neuritic plaque density and Braak neurofibrillary tangle stage – in patients with circle of Willis atherosclerosis[31] and not α-synuclein or TDP-43 lesion densities.[32]

SMALL VESSEL CEREBROVASCULAR DISEASE AND DEMENTIA

Small-vessel disease (SVD) is defined as a "syndrome of clinical, cognitive, neuroimaging, and neuropathological findings that are thought to arise from disease affecting the perforating cerebral arterioles, capillaries and venules and the resulting brain damage in the cerebral white and deep grey matter."[33]

SVD has been cited as the most common cause of vascular cognitive impairment.[34] In recent years, research has included vascular cognitive impairment in its breadth of focus as an umbrella term for cognitive decline with a vascular origin, and to denote a clinical syndrome that is both a precursor and risk factor for VaD.[35] SVD has been observed to be concomitant with AD pathology. In a recent study of an Asian population, Kandiah *et al*. demonstrated that the burden of white matter disease to be as high as 28% among patients with mild AD which increased to 39% among those with moderate-severe AD.[3] In a study conducted by Ye *et al*., there was an interactive effect between SVD biomarkers and baseline amyloid deposition in patients with subcortical VaD on measures of semantic word fluency, verbal memory, and global dementia severity.[36]

Four biomarkers of sporadic SVD will be discussed in this review paper: white matter hyperintensities, chronic lacunar infarcts, enlarged perivascular spaces, and cerebral microbleeds.

White matter hyperintensities

White matter hyperintensities (WMH) are abnormal areas of increased signal intensity on T2-weighted imaging and FLAIR where they present themselves as rounded or punctuate lesions - usually bilateral and symmetrically-distributed, which have a propensity to coalesce[33] (Figure 1). Pathologically, they represent areas of axonal degeneration, demyelination, and gliosis which may be secondary to hypoxia due to a compromised blood-brain barrier (BBB).[37] WMH can be used to predict cognitive deterioration and incident dementia, risk of future stroke, and mortality.[38,39] In a young-onset dementia cohort, moderate-to-severe WMH burden was associated with greater right medial temporal atrophy.[40]

While WMH has been linked with cerebrovascular risk factors, cognitive decline, and dementia, it is not pathognomonic of cognitive impairment as it can present itself in the cognitive-healthy elderly.[41]

Research has identified parenchymal blood flow to decline years before the onset of dementia. During which, evidence suggests that decreased cerebral perfusion is associated with increased WMH burden, especially deep-subcortical WMH[18,42] which is an independent predictor for conversion from mild cognitive impairment (MCI) to AD.[38] One possible mechanism is the chronic build-up of atherosclerosis in the intracranial arteries leading to reduced cerebral blood flow. The resultant hypoperfusion compromises the homeostatic environment of the surrounding neurons and glial cells, such as astrocytes and oligodendrocytes,[43] inducing gliosis and demyelination.

Chronic lacunar infarcts

Lacunes are small (3 – 15mm) cerebrospinal fluid-filled cavities in the brain caused by occlusion of the small deep penetrating arteries and can clinically-present themselves symptomatically or asymptomatically.[33] They appear isointense to CSF on T2-weighted imaging and FLAIR (Figure1). Cavitation occurs in approximately 28 – 94% of all acute lacunar infarcts. However, this figure is dependent on size, follow-up duration, and location of infarct.[33,44] Lacunes frequently occur along the edge of WMH that follow the course of small perforating arterioles. A longitudinal study of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) patients measured that 91.3% of incident lacunes were localized along the edge of a WMH.[45] Given such comorbidity, it is suspected that they share similar etiologies such as endothelial failure of the BBB.

Lacunes are associated with cognitive decline, incident dementia, and the pathogenesis of AD.[35] The association between lacunar infarcts and cognitive impairment is multifaceted; a single

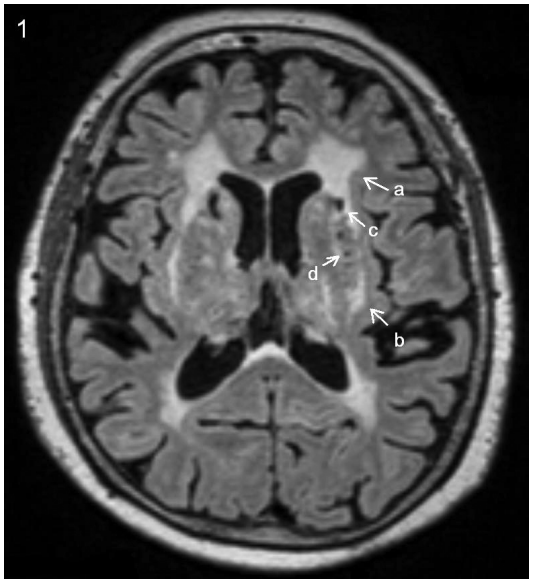

Figure 1. 80-year old female diagnosed with Alzheimer's disease. Fluid-attenuated inversion recovery (FLAIR) imaging reveals severe periventricular (a) and deep-subcortical (b) white matter hyperintensities, chronic lacunar infarct (c), and enlarged perivascular spaces (d)

infarct in a strategic location that is highly involved in cognitive function such as the thalamus[46], or multiple lacunar infarcts in tandem with deep-subcortical WMH and vascular risk factors as seen in subcortical VaD.[47]

Enlarged perivascular spaces

Enlarged perivascular spaces comprise of fluid-filled, likely interstitial[48] containments that surround the small perforating arterioles as they penetrate the brain parenchyma. They are less than 3mm in diameter and appear hyperintense on T2-weighted imaging or hypointense on FLAIR (Figure 1). Although sightings of enlarged perivascular spaces can be regarded as part of normal aging, an abnormally large amount suggests active inflammation. The activation of leukocytes in response to a local infection triggers an inflammatory reaction. This leads to disruption of the BBB and subsequent entry of leucocytes into the brain parenchyma. Perivascular spaces become dilated, owing to plasma fluid accumulation and eventually edema and tissue damage.[33,49] An increased number of enlarged perivascular spaces is frequently associated with greater WMH burden, signifying its relevance to SVD.[33] However, the location of enlarged perivascular spaces is important as it reflects different underlying etiologies; enlarged perivascular spaces in the basal ganglia are more reflective of hypertensive vasculopathy, while enlarged perivascular spaces in the white matter, particularly the centrum semiovale, are associated with cerebral amyloid angiopathy (CAA).[50]

The relationship between enlarged perivascular spaces and cognitive impairment is mixed. While some studies have observed a relationship with incident dementia at a 4-year follow-up[51] and poorer performances on non-verbal reasoning and visuospatial tasks[52], one study did not observe an association with cognitive impairment in a cohort of patients admitted for ischemic stroke or transient ischemic attacks.[53] However, the burden of enlarged perivascular spaces could have been overshadowed by the participants' comorbidity with acute ischemic incidents.

Cerebral microbleeds

Cerebral microbleeds are small deposits of hemosiderin secondary to compromised small vessel integrity. On T2*-weighted gradient-recalled echo or susceptibility-weighted imaging, they appear as small (2 – 5mm), rounded, well-defined, and homogenous foci of low signal intensity (Figure 2). Location of cerebral

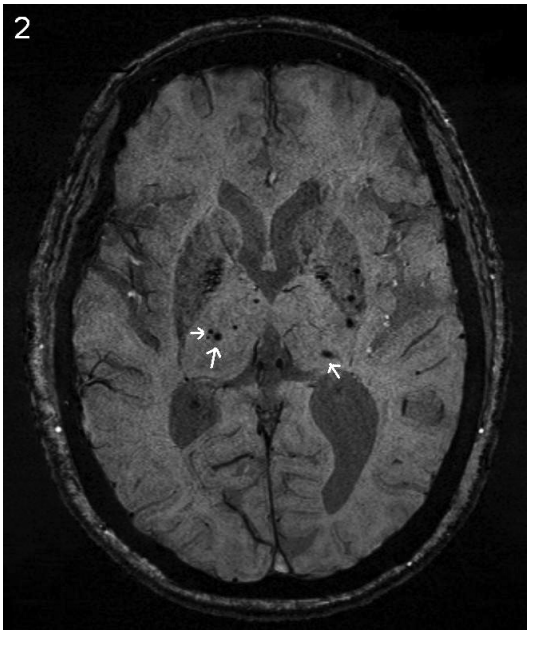

Figure 2. 68-year old female diagnosed with Alzheimer's disease. Susceptibility-weighted imaging (SWI) reveals multiple microbleeds in the putamen, thalamus, and internal capsule. Symmetrical hypointensities in the globus pallidus are likely to reflect calcifications

microbleeds reflects different underlying etiologies; those located in deep and infratentorial regions of the brain are associated with hypertensive or atherosclerotic microangiopathy, while lobar ones are associated with CAA.[54]

Cerebral microbleeds are frequently seen in AD as it is prevalent in approximately one-third of cases with clinical presentations of the disease.[55] While increased burden of cerebral microbleeds is associated with poorer performance on neuropsychological testing, cognitive decline, and progression from MCI to non-AD dementia[54], its specific role in progression to AD has yet to be elucidated.[56] Several hypotheses have attempted to explain how cerebral microbleeds might influence cognition, but determination has remained inconclusive. Charidimou and Werring[57] propose that cerebral microbleeds could: 1) exact direct structural damage or 2) functional disturbance to surrounding brain; or 3) through induction of arterial stenosis and resultant hypoperfusion.

ROLE OF MANAGING RISK FACTORS

It has been estimated that half of AD and dementia cases are attributable to potentially modifiable risk factors like the cerebrovascular risk factors, depression, and physical and cognitive inactivity.[7] At a population level, the Alzheimer's Association has concluded that healthy behaviors like regular physical exercise, management of vascular risk factors, healthy diet, lifelong learning and cognitive training are not only effective for diabetes, CVD, and cancer, but also reduce the risk of cognitive decline.[58] The Rotterdam study showed that up to one-third of dementia cases can be prevented through optimal prevention and treatment of cerebrovascular risk factors.[59]

Lifestyle modification and diet

Lifestyle modification has been the primary target in preventing the development of CVD. Adherence to the Mediterranean diet was associated with better cognition, lower rate of cognitive decline, and lower risk of developing AD.[60] The FINGER study – a multi-domain lifestyle-based intervention including nutritional guidance, physical and cognitive exercise, social activity, and intensive monitoring and management of the cerebrovascular risk factors– showed beneficial effects to cognitive functions in the intervention group compared with placebo.[61]

Weight loss was noted to have a beneficial effect on memory, attention, and executive function in overweight and obese subjects. The magnitude of the effect was directly associated with baseline BMI.[62] A 25% reduction in midlife obesity prevalence could potentially lower AD prevalence by more than 166,000 cases worldwide.[7]

Hypertension

In the Systolic Hypertension in Europe (Syst-Eur) trial, a reduction in dementia cases was found in subjects treated for isolated systolic hypertension[63] and an increasing systolic blood pressure in midlife was associated with a more rapid increase in WMH volume.[64] Another study showed that elevated diastolic blood pressure is associated with poorer cognitive function in individuals older than 50 years and may also be associated with age-related cognitive decline.[65] The Eight Joint National Committee (JNC 8) recommends pharmacologic treatment for systolic blood pressure of 150mmHg or higher, or when diastolic pressure is 90 mmHg or higher for adults 60 years and older; and 140 mmHg or higher, or when the diastolic pressure is 90 mmHg or higher in younger than 60 years old.[66] If the prevalence of midlife hypertension were 25% lower than current levels, it has been estimated that there would be more than 400,000 fewer AD cases worldwide.[7]

Diabetes mellitus

Elderly subjects with newly diagnosed DM are found to have significantly higher risk of dementia independent of pre-existing coronary artery disease, CVD, hypertension, and chronic kidney disease.[67] A 12-year population-based cohort study found that the diabetic complication severity and the change in severity were associated with an increased incidence of dementia in new-onset diabetic patients.[68] Poorly-managed DM can also exacerbate dementia ad cognitive impairment possibly through hyperglycemia and hypoglycaemia.[69] If DM prevalence was lowered by 25%, more than 200,000 AD cases worldwide could potentially be prevented worldwide.[7]

Smoking

Smoking is also associated with poorer cognitive function in individuals older than 50 years and may also be associated with age-related cognitive decline.[65] Quitting smoking or former smokers did not show increased risk compared to smokers[70] and middle-aged male smokers were likely to experience faster 10-year cognitive decline in global cognition and executive cognition

compared to abstainers.[71] Globally, a 25% reduction in smoking prevalence could potentially lower AD prevalence by more than 1 million.[7]

ROLE OF STATINS

Research on statins in reducing dementia remains inconclusive. A review by Daneschvar *et al*.,[72] which included the Sacramento Area Latino Study on Aging (SALSA), AD Anti-inflammatory trial (ADAPT), Rotterdam Study, and Religious Orders study, showed that statins do reduce the risk for dementia. On the other hand, another systematic review on statins by the Cochrane Collaboration, which included the PROSPER trial, showed that statins have no effect on preventing dementia.[73]

ROLE OF ANTIPLATELETS

Aspirin

The potential benefits of aspirin therapy are reduction of risk of coronary disease and stroke. In a randomized clinical trial of low dose aspirin, it showed that aspirin can reduce the risk of myocardial infarction and stroke, slow the onset or progression of dementia, and improve quality of life among elderly individuals although the results were possibly offset by the increase in intracerebral hemorrhages and gastrointestinal bleeding among elderly subjects.[74] Another randomised placebo-controlled trial of women aged 65 years and above did not show any significant difference in terms of overall performance and the average cognitive decline during the 3-6 year follow-up.[75]

Cilostazol

Cilostazol has been shown to decrease beta-amyloid accumulation and protect beta-amyloid-induced cognitive deficits in an experimental model.[76] It can also promote the differentiation and survival of newly-generated oligodendrocytes, which results in enhanced remyelination followed by functional recovery.[77] A pilot study that compared cilostazol against clopidogrel with aspirin as a control showed that subjects randomized under cilostazol did not show deterioration in neuropsychological scores after 6 months as compared to the control group. There was also improvement in the regional cerebral blood flow in the thalamus, inferior frontal, left middle frontal, left medial frontal, angular, superior temporal, middle temporal, inferior temporal, anterior cingulate, and left posterior cingulate gyri.[78] In a multivariate analysis, it also showed that cilostazol was a significant predictor of slower cognitive decline as measured by MMSE.[79] A retrospective study found that cilostazol has the potential to preserve cognitive function in patients with MCI for 1 year on average.[80] The latter two studies showed that cilostazol improved performance on orientation to time, place, and delayed recall tasks.

CONCLUSION

CVD is increasingly being demonstrated to influence the incidence, prevalence, and progression of dementia. Greater emphasis on managing CVRF starting from midlife should be made a priority worldwide, especially in developing countries where an epidemic of dementia is looming.CVD risk factors are also of particular relevance to the Asian population where a high burden of small vessel CVD has been demonstrated in Asian patients with dementia.

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